DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

DATE: April 14, 2008

TO: Randall W. Lutter, Ph.D.
Deputy Commissioner for Policy
Food and Drug Administration

THROUGH: Vince Tolino /S/
Director, Ethics and Integrity Staff
Office of Management Programs
Office of Management

Michael F. Ortwerth, Ph.D. /S/
Deputy Director, Advisory Committee Oversight and Management Staff
Office of Policy, Planning, and Preparedness

FROM: Igor Cerny, Pharm.D. /S/
Director, Advisors and Consultants Staff
Center for Drug Evaluation and Research

SUBJECT: 712(c)(2)(B) Conflict of Interest Waiver for Thomas Bersot, M.D., Ph.D.

I am writing to request a waiver for Thomas Bersot, M.D., Ph.D., a Member of the Endocrinologic and Metabolic Drugs Advisory Committee, from the conflict of interest prohibitions of section 712(c)(2)(A) of the Federal Food, Drug, and Cosmetic Act. Waivers under section 712(c)(2)(B) may be granted by the appointing official where it is "necessary to afford the advisory committee essential expertise" and where the individual has made a disclosure to FDA of the financial interests at issue. We have determined that you are the appointing official for purposes of section 712(c)(2)(B). Therefore, you have the authority to grant Dr. Bersot a waiver under section 712(c)(2)(B).

Section 712(c)(2)(A) prohibits Federal executive branch employees, including special Government employees, from participating in any particular matter in which the employee or an immediate family member has a financial interest that could be affected by the advice given to the FDA with respect to the matter. Because Dr. Bersot is a special Government employee, he is under a statutory obligation to refrain from participating in any deliberations that involve a particular matter having a direct and predictable effect on a financial interest attributable to him.

The function of the Endocrinologic and Metabolic Drugs Advisory Committee is to review and evaluate available data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of endocrine and metabolic disorders and to make appropriate recommendations to the Commissioner of Food and Drugs.

Dr. Bersot has been asked to participate in the July 1-2, 2008, meeting to discuss the role of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for the treatment of type 2 diabetes mellitus.

This matter is coming before a meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. This issue is a particular matter involving specific parties.

Dr. Bersot has advised the Food and Drug Administration (FDA) that his spouse has a current financial interest which could potentially be affected by his participation in the matter described above. Dr. Bersot's spouse owns stock in ------. ------ is an affected firm for this meeting.

As a Member of the Endocrinologic and Metabolic Drugs Advisory Committee, Dr. Bersot could become involved in matters that could affect his financial interest. Under section 712(c)(2)(A), he is prohibited from participating in such matters. However, as noted above, you have the authority under section 712(c)(2)(B) to grant a waiver permitting Dr. Bersot to participate in such matters if necessary to afford this committee essential expertise.

For the following reasons, I believe that it would be appropriate for you to grant a waiver to Dr. Bersot that would allow him to participate fully in the matters described because his voting participation is necessary to afford the committee essential expertise.

First, Dr. Bersot's stock interest is not so substantial as to preclude his participation in the matters coming before the committee. ------ is a large, well-established firm with multiple product lines and global presence. It is unlikely that the committee's recommendations concerning the role of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for the treatment of type 2 diabetes mellitus will significantly impact the economic stability of the company.

Second, according to the Review Division, the uniqueness of Dr. Bersot's qualification justifies granting this waiver. The topic of discussion is cardiovascular risk assessment in the approval process for anti-diabetic agents. Over the past few years, and recently after the rosiglitazone issue, there has been much public debate surrounding the need for cardiovascular outcomes data for an anti-diabetic agent. The debate is quite divided with advocates for such data arguing that requiring such studies will improve knowledge on the efficacy and safety of a drug. Critics of such a position have argued that the requirement of such costly clinical trials would slow down the availability of effective therapies targeting treatment of hyperglycemia, a surrogate that has direct impact on other complications in diabetes aside from cardiovascular. It is important to note that treatment of diabetes targets normal glycemic control to reduce many risks, microvascular and macrovascular. Over the past several decades, evidence that good glycemic control reduces the risk of microvascular complications such as kidney failure, blindness, and neuropathy is extensive from several large clinical trials.

Diabetes is undoubtedly a risk factor for cardiovascular disease with patients experiencing a 2 to 4-fold risk of having a cardiovascular event. This known fact has resulted in the National Cholesterol Education Program (NCEP), the American Diabetes Association, and other leading medical organizations recommending aggressive lipid-lowering treatment of a diabetic patient

regardless of a history of a clinical cardiovascular event. A complex aspect of designing a cardiovascular outcome trial in the diabetic population is the adequate control of multiple risk factors, of which, cholesterol levels will be a frontline consideration. The results of some recent cardiovascular studies of anti-diabetic therapies have been criticized for imbalances in lipid management. The importance of lipid management is underscored in some ongoing trials which have established separate Steering Committees to ensure intensive control of lipids levels.

Dr. Bersot is the only lipidologist on the panel and his basic and clinical research experience in this area will undoubtedly be called upon in the design and conduct of any diabetes regimen, especially those that may have an impact on lipid biology. I believe that participation by Dr. Bersot in the committee's deliberations will contribute to the diversity of opinions and expertise represented on the committee.

Lastly, locating qualified individuals without disqualifying financial interest to serve on this advisory committee has been very difficult. This meeting touches not only on the approval of therapies for diabetes management but on cardiovascular risk in this patient population, interventions to reduce this risk, and complex study designs. As such, the meeting will require the participation of a multi-disciplinary committee including endocrinologists/diabetologists, cardiologists, and biostatisticians. The Division of Metabolism and Endocrinology Products contacted all current members of its advisory committee, Special Government Employees (SGEs)/past members, and outside researchers/clinicians with expertise in lipid biology. There are three members/SGEs meeting this criterion and only Dr. Bersot was available for the date of this meeting. The Division also inquired of the availability of the co-chair of National Institutes of Health (NIH), National Cholesterol Education Program (NCEP). He was not available to participate in the advisory committee meeting. To that end, the Division requests that a waiver be granted for Dr. Thomas Bersot to participate as there has been a genuine effort to secure individual participation and representation with minimal conflict of interest.

Moreover, the Federal Advisory Committee Act requires that committee memberships be fairly balanced in terms of the points of view represented and the functions to be performed by the advisory committee. Also, the committee's intended purpose would be significantly impaired if the agency could not call upon experts who have become eminent in their fields, notwithstanding the financial interests and affiliations they may have acquired as a result of their demonstrated abilities. Dr. Thomas Bersot is board-certified in internal medicine and is currently a Professor of Medicine at the University of California in San Francisco (UCSF) and is an expert in lipid biology. He has had extensive training in this field through several renowned academic institutions including the National Institutes of Health's National Heart Lung, and Blood Institute.

Accordingly, I recommend that you grant Thomas Bersot, M.D., Ph.D., a waiver that would allow his voting participation in all official matters concerning the role of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for the treatment of

type 2 diabetes mellitus. I believe that such a waiver is appropriate because in this case, Dr. Bersot's voting participation is necessary to afford the committee essential expertise.

DECISION:

X Waiver granted based on my determination, made in accordance with section 712(c)(2)(B) of the Federal Food, Drug, and Cosmetic Act, that voting participation is necessary to afford the committee essential expertise.

___ Waiver granted based on my determination, made in accordance with section 712(c)(2)(B) of the Federal Food, Drug, and Cosmetic Act, that nonvoting participation is necessary to afford the committee essential expertise

___ Waiver denied.

/s/ 6/13/08

Randall W. Lutter, Ph.D. Date
Deputy Commissioner for Policy
Food and Drug Administration